REMARKS

General

Applicants thank the Examiner for extending the courtesy of an in-person interview on December 14, 2005. Applicants believe that the response that was filed on December 23, 2005, failed to reach the Examiner prior to his issuing the Office Action dated December 29, 2005. Therefore, this response is contains portions of the December 23, 2005, response and addresses the new grounds as well.

The Invention.

The present invention provides modified forms of pullulanase which maintain the ability to catalyze the hydrolysis of an alpha-1,6-glucosidic bond, compositions which comprise the modified pullulanase, methods of making the modified pullulanase and methods of using the modified pullulanase, especially for the saccharification of starch.

Status of the Application.

Claims 5-10, 12, 14, 15, 27-40 and 52-66 are pending in the application.

Claims 5-10, 12, 14, 15, 27-40 and 52-66 are rejected.

No claims have been amended herein.

35 U.S.C. §103.

The Examiner has rejected claims 5–10, 12, 14, 15, 27–29, 31–40, 52–53, 55-61 and 63–66 as allegedly obvious. The Examiner has cited at least one of three references in the §103 rejections. Applicants respectfully traverse the rejection(s).

"This rejection is based on printed publications and a patent." See June 29, 2005 Office Action, page 3. Similar statements were offered in all of the previous Office Actions asserting unpatentability under 35 USC §103. See March 30, 2005 Office Action, page 3; May 4, 2004 Office Action, page 6; January 27, 2003 Office Action, page 3; and February 12, 2002 Office Action, page 5. There was no §103 rejection in the October 17, 2003 Office Action; the response dated July28, 2003, having successfully presented a persuasive argument that the claims were non-obvious. Thus, *Applicants need only show why the cited publications and patent do not render the presently*

claimed invention obvious in light of these three documents as there has been no notice that any other evidence is being relied upon.

Applicants have provided a summary of the art in their response dated May 17, 2005, and is supplemented below. Therefore, the information below should be read in conjuction with the previous summary.

Deweer, et al. (US Pat. No. 6,074,854)

There is no teaching or suggestion to look for biologically active pullulanase fragments in Deweer *et al.*.

There is nothing in Deweer *et al.* that would suggest to or motivate the skilled artisan to truncate the *Bacillus* pullulanase or to combine its teachings with McPherson *et al.* or Albertson *et al.*

McPherson et al. (Biochemical Soc. Trans., (1988) 16(5):723-724)

The Examiner cites McPherson *et al.* as teaching proteolytic digestion, computer-based sequence analysis, and that the long N-terminal region lacks any catalyzing site. See page 4 of the Office Action.

Applicants note that McPherson *et al.* at best teaches that there may be some length of "the N-terminal region of pullulanase that has no defined catalytic function" for the *Klebsiella* pullulanase. ***There is no suggestion that the lack of defined catalytic function found in Klebsiella would be similarly found in an unrelated and non-homologous pullulanase.*** In addition, it is silent on whether or not other truncated pullulanases, in particular *Bacillus* pullulanases, would possess similar properties, characteristics or corresponding increases in activity.

There simply is no motivation to combine McPherson *et al.* with any of the cited art.

Albertson et al., (Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39)

The Examiner cites Albertson *et al.* (Cloning and sequence of a type I pullulanase from an extremely thermophilic anaerobic bacterium, *Caldicellulosiruptor saccharolyticus.* Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39) as teaching

the modification of a pullulanase isolated from *C. saccharolyticus*, wherein nearly 381 nucleotides from the 5' region of the cDNA encoding a pullulanase and that the deleted amino acid sequence is not essential for either activity or thermostability. See page 4 of the Office Action.

Applicants note that the work in Albertson *et al.* is related to "the molecular cloning of the gene ... and determination of its DNA and **predicted** amino acid sequence." (Emphasis added.)

The "truncation" of Albertson *et al.* may not have been a true truncation. The functional "truncated" pullulanase may be in fact be the full-length enzyme, the result of an internal start sequence. See page 38, top of column 1 where it states:

> "A possible internal start sequence complete with a ribosomal binding site could also be detected internally within the pullulanase gene (see Fig. 2), and this feature may explain the occurrence of enzymatic activity from the incomplete recombinant plasmid pNZ1452."

Applicants note that even if the truncated enzyme of Albertson *et al.* has a truncation of 95 amino acids (see page 38, top of column 2) from its N-terminus, this is fewer than the smallest truncation currently claimed. There is no suggestion or teaching that a longer deletion in an unrelated molecule would result in a functional enzyme.

Claims 5–10, 14, 15, 27–40, 52–61 and 63–66

The Examiner has rejected claims 5–10, 14, 15, 27–40, 52–61 and 63–66 as allegedly obvious over the combination of Deweer, *et al.* (US Pat. No. 6,074,854) in view of McPherson *et al.* (Biochemical Soc. Trans., (1988) 16(5):723-724) or Albertson *et al.*, (Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39). Applicants respectfully traverse the rejection.

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the references to arrive at the

claimed invention. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990)

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicants to withdrawal of the rejection of the claims in issue.[1] Applicants urge that the Examiner has failed to establish at least one of the requirements as discussed below.

The Deweer/McPherson combination

Deweer *et al.* is silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed. McPherson *et al.* is similarly silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed.

The combination fails to suggest or motivate one of skill in the art to modify the teachings to yield the claimed invention

The Examiner asserts that "it appears that experiments involving truncation of N-terminal amino acids in pullulanase enzymes was well known in the art." See page 4 of the Office Action. Applicants note that McPherson *et al.* states "The predicted amino acid sequences of pullulanases from *Klebsiella pnuemoniae* strains W70 ...and FG9 ... are very similar and provide the basis for the design of experiments to examine pullulanase function." Thus, the similarity in the protein sequences was critical to

designing experiments to define a functional 'core' pullulanase. However, there is very little sequence similarity between the presently claimed pullulanase and the pullulanase of McPherson *et al.* Thus, **one of skill in the art would not be motivated to combine McPherson *et al.* with DeWeer due to the lack of similarity between the pullulanases.**

The combination fails to disclose the elements of the claimed invention

The currently presented claims are directed to: (a) a truncated *Bacillus* pullulanase comprising (b) a deletion of about 100 amino acids from the amino terminus of a pullulanase (c) obtainable from *Bacillus deramificans*, wherein said truncated pullulanase comprises (d) a conserved Y region, and (e) is capable of catalyzing the hydrolysis of an alpha-1, 6-glucosidic bond.

As noted above, there is no mention of a deletion of about 100 amino acids from the amino terminus of a pullulanase obtainable from *Bacillus deramificans* in either Deweer *et al.* or McPherson *et al.* Although McPherson *et al.* describes a deletion of 170 amino acids that is in an unrelated gram-negative bacterial pullulanase, not in a *Bacillus* pullulanase. Therefore, the combination fails to disclose at least two of the elements of the presently claimed invention.

The combination fails provide a reasonable expectation of success

As previously stated, a skilled artisan would not have a reasonable expectation of success if they were to combine the references. First, there is nothing in Deweer *et al.* that indicates that a truncation of 98, 100, 102, 200 or 300 amino acids would result in an enzyme capable of catalyzing the hydrolysis of an alpha-1, 6-glucosidic bond.

Although McPherson *et al.* does teach a 170 amino acid deletion in an unrelated pullulanase there is no information provided that would allow the skilled artisan to perform a sequence alignment with a *Bacillus* pullulanase to know whether or not a similarly large deletion would work. **Notably, as noted above, McPherson *et al.* relied**

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[1] *See e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

on the similarity between known enzymes to design their experiments. The *Klebsiella* pullulanase of McPherson *et al.* is 120 kD whereas a *Bacillus* pullulanase is smaller. A similarly large deletion in the smaller enzyme may not work. Furthermore, there is no teaching that an even larger deletion would work. Thus, there is no reasonable expectation of success given the dissimilarity of the pullulanases in Deweer *et al.* and McPherson *et al.*.

For the foregoing reasons, the combination of Deweer *et al.* and McPherson *et al.* is inappropriate and fails to render the present invention obvious. Withdrawal of the rejection is respectfully requested.

The Deweer/Albertson combination

Deweer *et al.* is silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed. Albertson *et al.* is similarly silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed. Moreover, **the Albertson *et al.* "truncated" pullulanase may not have in fact been truncated**, see *supra*.

The combination fails to suggest or motivate one of skill in the art to modify the teachings to yield the claimed invention

In addition to the arguments presented in their response dated May 17, 2005, Applicants assert that the uncertainty of whether or not there was a "truncated" protein in Albertson *et al.* would not motivate a skilled artisan to intentionally truncate a full-length protein.

The combination fails to disclose the elements of the claimed invention

As noted above, the currently presented claims are directed to: (a) a truncated *Bacillus* pullulanase comprising (b) a deletion of about 100 amino acids from the amino terminus of a pullulanase (c) obtainable from *Bacillus deramificans*, wherein said truncated pullulanase comprises (d) a conserved Y region, and (e) is capable of catalyzing the hydrolysis of an alpha-1, 6-glucosidic bond.

Applicants contend the combination of references does not contain a teaching of a truncated pullulanase from a *Bacillus* species wherein the truncated enzyme retains the capacity to hydrolyze alpha-1,6-glucosidic bonds. Deweer *et al.* and Albertson *et al.* taken together do not disclose (b) a deletion of about 100 amino acids from the amino terminus of a pullulanase nor (d) a conserved Y region.

There is no teaching in either Deweer *et al.* or Albertson *et al.* that a *Bacillus* pullulanase could comprise a deletion of about 98, 100, 102, 200 or 300 amino acids from the amino terminus. If one were to use the alignment provided by Albertson *et al.* in Figure 2 (page 37 of Albertson *et al.*) for *Caldicellulosiruptor saccharolyticus* and *Bacillus acidopullulolyticus*, the 95 amino acid deletion in *C. saccharolyticus* would correspond to amino acid residue 137 in *B. acidopullulolyticus*. At best, this is an invitation to try, an inappropriate test for obviousness.

As taught by the Applicants at page 12 of the specification, Albertson *et al.* reveal the regions called DPY, A, B, C, D, E, and YNWGY as conserved regions among a group of gram-positive and gram-negative pullulanases. Two regions, DPY and YNWGY were identified as being characteristic of true pullulanases (although Applicants note that the *Thermus* sp AMD33 pullulanase shown in Figure 2 on page 37 lacks a DPY region). In addition to the conserved regions highlighted by Albertson *et al.*, Applicants significantly disclose two other conserved regions closer to the N-terminus of pullulanase. These regions are referred to as Y and VWAP and reference is made Figures 2A – 2D of the specification. Interestingly, the VWAP region, although clearly shown in Figure 2 on page 37 of Albertson *et al.* is not taught or suggested by Albertson

et al., as being a region of any importance. Applicants further disclose that the limits of amino acid truncations in the N-terminus of pullulanase would not go beyond the Y region, a small region (i.e., less than 6 amino acids in length) that was also not commented on by Albertson *et al.*

Therefore, the cited art combination fails to teach or disclose the claimed invention.

The combination fails provide a reasonable expectation of success

Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. See *Micro Chem.*, 103 F.3d at 1547, 41 U.S.P.Q.2D (BNA) at 1245.

Applicants once again direct the Examiner's attention to the teachings of Albertson *et al.* to the fact that the "truncation" may be due to an internal start sequence and therefore was in fact a full-length protein. A skilled artisan would not have a reasonable expectation of success that truncating a full-length, unrelated protein would yield a functional enzyme based on the work in Albertson *et al.*

Claim 12

The Examiner has rejected claim 12 as allegedly obvious over of Deweer, *et al.* (US Pat. No. 6,074,854). The Examiner asserts that the cited reference teaches the claimed invention. Applicants respectfully traverse.

There is no teaching or suggestion in any of the cited references to specifically add an alanine to the N-terminus. While, as the Examiner notes, that there are only twenty amino acids not one of the cited references point directly to adding an alanine.

Withdrawal of the rejection is respectfully requested.

Double Patenting.

Claims 5-10, 12, 14, 15, 27-40 and 52-66 stand rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 3 and 4 of U.S. Patent No. 6,074,854 in view of McPherson et al. (Biochemical Soc. Trans., 1988, vol 16(5):723-724) or Albertson et al., (Biochim. Biophys. Acta, Vol.

1354:35-39, 1997)." Applicants respectfully traverse.

Applicants read the Examiner's rejection as McPherson and Albertson providing the level of ordinary skill in the pertinent art.

According to the MPEP, Section 804:

> Any obvious-type double patenting rejection should make clear:.
>
> (A) The differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

Applicants note that the Examiner's statement that "While claims 3 and 4 of the patent are drawn to the pullulanase with SEQ ID NO:11/12, encoded by SEQ ID NO:10 and isolated from a *B. deramificans* strain, claims 5-10, 12, 14-15, 27-40, 52,66 of the instant application are also drawn to the very same enzyme **but to truncated form of the same.**" (Emphasis added.) Applicants believe that this is a clear indication that there is a difference between the instant claims and the '854 claims.

In addition, the Examiner fails to point to a disclosure in the '854 patent that provides support for the assertion that "the enzyme includes several embodiments that would indeed anticipate or render obvious the trunctated forms claimed in claims 5-10, 12, 14, 15, 27-40, 52-66." See page 10, lines 15-18, of the December 29, 2005 Office Action. There is only the nebulous reference "The portion of the specification (and the claims)" as support.

Finally, for the reasons stated above, Applicants believe that the McPherson and Albertson references fail to provide the basis for the assertion that the present claims are an obvious variation of the invention defined in the '854 patent.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,

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